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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,476	09/30/2003	Robert B. DuBridge	181 US UT01	7526

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,476	DUBRIDGE, ROBERT B.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *20-26 and 30-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/04, 3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-65 are pending in the instant application.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-19 and 27-29) in the reply filed on 3/18/2005 is acknowledged.

During a telephone conversation with Stacy Landry on 5/5/2005 a provisional election was made of Flp recombinase, without traverse, as the elected recombinase activity of the rec element as per the species election requirement on pages 4-5 of the prior Office action. Affirmation of this election must be made by applicant in replying to this Office action.

Claims 20-26 and 30-65 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. An examination on the merits of claims 1-19 and 27-29 follows.

Information Disclosure Statement

Receipt of information disclosure statements, filed on 8/13/2004 and 3/24/2005, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Figure 10 is not

described in the specification in the brief description of the drawings section. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 8 is objected to because of the following informalities: the claim recites a "cellular expression of Claim 1" whereas it should recite a "cellular expression system of Claim 1." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 10, 12, 16 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7, 10, 12, 16 and 28 are vague and indefinite in that the metes and bounds of the term "TAG sequence" are unclear. The term is unclear in that it can be interpreted literally as the nucleic acid sequence "TAG" which could potentially be utilized as a stop codon. Alternatively, the term can be interpreted as a sequence encoding a tag such as an epitope tag. It would be remedial to amend the claim language to clearly indicate the structural features of the claimed sequence.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 5 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Bode et al (EP 0939120 A1; see the entire reference).

Regarding claim 1, Bode et al teach the claimed first integration cassette, first target cassette and rec element. Bode et al teach a first integration cassette (Tag) comprising a promoter operably linked to a hygtk fusion gene (scorable homeostatic reporter element), wherein the promoter and fusion gene are flanked by a first recombinase recognition site (F_3) at the 5' end and a second recombinase recognition site (F) at the 3' end (e.g. Abstract; Figure 1;

paragraphs [0013]-[0017], [0028]). The first integration cassette is capable of randomly integrating into the genome of a cell (e.g. Figures 1 and 2; paragraph [0013]). Bode et al teach a first target cassette (exchange vector) comprising a third recombinase recognition site (F_3), a neomycin coding sequence (target element), and a fourth recombinase recognition site (F) (e.g. Table 1; Figure 1; paragraphs [0013]-[0017] and [0020]). Bode et al teach a rec element, *flp*-F7OL, encoding a recombinase polypeptide capable of catalyzing a recombination reaction between the wild type FRT sites (F) and between mutant FRT sites (F_3) (e.g. paragraph [0020]).

Regarding claim 4, Bode et al teach the use of Flp recombinase (e.g. Abstract; paragraphs [0010] and [0017]).

Regarding claim 5, Bode et al teach the random integration of the first integration cassette (Tag) into murine embryonic stem cells (i.e. mammalian cells) (e.g. paragraphs [0015] and [0028]).

Regarding claim 27, Bode et al teach a first integration cassette (Tag) comprising a promoter operably linked to a hygtk fusion gene (scorable homeostatic reporter element), wherein the promoter and fusion gene are flanked by a first recombinase recognition site (F_3) at the 5' end and a second recombinase recognition site (F) at the 3' end (e.g. Abstract; Figure 1; paragraphs [0013]-[0017], [0028]). The first integration cassette is capable of randomly integrating into the genome of a cell (e.g. Figures 1 and 2; paragraph [0013]).

Claims 1, 4, 5, 8 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Seibler et al (Biochemistry, Vol. 36, pages 1740-1747, 1997; see the entire reference).

Regarding claim 1, Seibler et al teach the claimed first integration cassette, first target cassette and rec element. Seibler et al teach a first integration cassette (P construct) comprising an FTR site interposed between an SV40 promoter and a bicistronic expression unit consisting of the SEAP and HygTk genes followed by a second FRT site different from the first FRT site (e.g. Figure 2; paragraph bridging pages 1742-1743). The first integration cassette is capable of random integration into the genome of a cell (e.g. page 1741, *Transfection (Stable Expression)*). Seibler et al teach a first target cassette (promoter-free exchange plasmid) comprising a bicistronic expression unit, consisting of the luciferase and puromycin resistance genes, flanked by FRT sites capable of recombining with the first and second FRT sites of the first integration vector (e.g. Figure 2; paragraph bridging pages 1742-1743). Seibler et al teach plasmid pOG44, a rec element encoding flp recombinase (e.g. page 1741, *(d) Recombination Prior to Integration*).

Regarding claim 4, Seibler et al tech the use of a Flp recombinase activity (e.g. Table 1; Figure 1; page 1741, *(d) Recombination Prior to Integration*).

Regarding claim 5, Seibler et al teach the use of mammalian cells (e.g. Figure 3).

Regarding claim 8, Seibler et al teach a first target element (luciferase) further comprising a selectable marker gene (puromycin resistance).

Regarding claim 27, Seibler et al teach the claimed first integration cassette, first target cassette and rec element. Seibler et al teach a first integration cassette (P construct) comprising an FTR site interposed between an SV40 promoter and a bicistronic expression unit consisting of the SEAP and HygTk genes followed by a second FRT site different from the first FRT site (e.g.

Figure 2; paragraph bridging pages 1742-1743). The first integration cassette is capable of random integration into the genome of a cell (e.g. page 1741, *Transfection (Stable Expression)*).

Claims 1-3, 5, 8 and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Ow (US Patent Application Publication No. 2002/0123145; see the entire reference).

Regarding claim 1, Ow teaches the claimed first integration cassette, first target cassette and rec element. Ow teaches a first integration cassette (receptor construct) comprising a promoter operably linked to a first exchangeable reporter segment comprising a thymidine kinase (tk) coding region (scorable homeostatic reporter element) and a zeocin resistance coding region (exchangeable reporter gene), wherein the tk coding sequence is linked to a first recombinase recognition site (PP') at its 5' end and to a second recombinase recognition site at its 3' end (PP') (e.g. Figure 4). More generally, Ow teaches integration cassettes comprising a polynucleotide flanked by two irreversible recombination sites (IRSs), which are stably integrated into the genome of a host organism (e.g. paragraphs [0014] and [0042]). Because the cassettes do not comprise sequence homologous to a chromosome of the target organism, integration will be random. Ow teaches a first target cassette (donor construct) comprising a third recombinase recognition site (BB'), capable of recognizing the first recognition site in the first integration cassette; a first target element (cDNA); and a fourth recombinase recognition site (BB'), capable of recognizing the second recombinase recognition site in the first integration cassette (e.g. Figure 4). More generally, Ow teaches target cassettes comprising a polynucleotide flanked by two irreversible complementary recombination sites (CIRSs) (e.g. paragraphs [0014] and [0042]). Ow teaches a rec element encoding a recombinase polypeptide capable of catalyzing a

recombination reaction between IRS and CIRS, wherein introduction of the rec element and the first target cassette to the recombinant cell population comprising the first integration cassette results in site-specific substitution of the first exchangeable reporter segment with the first exchangeable target segment (e.g. Figure 4, paragraphs [0014], [0037] and [0054]).

Regarding claim 2, Ow teaches that the rec element (polynucleotide encoding the recombinase) can be included in the first integration cassette (receptor construct) containing the IRSs (e.g. paragraphs [0045] and [0054]).

Regarding claim 3, Ow teaches that the rec element can be included in the first target cassette (donor construct) containing the CIRSs (e.g. paragraph [0054]).

Regarding claim 5, Ow teaches the use of the abovementioned system in host cells such as mammalian cells, fungi and bacteria.

Regarding claim 8, Ow teaches a first target element further comprising a first target gene and a first selectable marker gene (e.g. paragraphs [0060] and [0180]).

Regarding claim 27, Ow teaches a first integration cassette (receptor construct) comprising a promoter operably linked to a first exchangeable reporter segment comprising a thymidine kinase (tk) coding region (scorable homeostatic reporter element) and a zeocin resistance coding region (exchangeable reporter gene), wherein the tk coding sequence is linked to a first recombinase recognition site (PP') at its 5' end and to a second recombinase recognition site at its 3' end (PP') (e.g. Figure 4). More generally, Ow teaches integration cassettes comprising a polynucleotide flanked by two irreversible recombination sites (IRSs), which are stably integrated into the genome of a host organism (e.g. paragraphs [0014] and [0042]).

Because the cassettes do not comprise sequence homologous to a chromosome of the target organism, integration will be random.

Claims 27-29 are rejected under 35 U.S.C. 102(e) as being anticipated by Cheo et al (US Patent Application Publication No. 2002/0007051; see the entire reference).

Regarding claim 27, Cheo et al teach an integration cassette (e.g. starting molecule or Destination vector) comprising two recombination sites flanking promoters, selectable markers, and tags such histidine tags or green fluorescent protein (e.g. paragraphs [0050], [0147], [0148], [208] and [0488]; Figure 6). Further, Cheo et al teach the addition of regions that allow integration into eukaryotic chromosomes (e.g. transposable elements) (e.g. paragraph [0327]).

Regarding claim 28, Cheo et al teach the use of tagged proteins such as his tags (e.g. paragraph [0050]). Further, Cheo et al teach the use of recombination sites that comprise att sites, which comprise a TAG nucleic acid sequence (e.g. paragraph [0049]).

Regarding claim 29, Cheo et al teach the use of internal ribosome entry sites (IRES) to make bi-cistronic expression elements where two structural genes are expressed from a single promoter (e.g. paragraphs [00147] and [0544]).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-19 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo et al (US Patent Application Publication No. 2002/0007051; see the entire reference) in view of Seibler et al (Biochemistry, Vol. 36, pages 1740-1747, 1997; see the entire reference).

Regarding claim 1, Cheo et al teach an integration cassette (e.g. starting molecule or Destination vector) comprising two recombination sites flanking promoters, selectable markers, and tags such histidine tags or green fluorescent protein (e.g. paragraphs [0045], [0050], [0147], [0148], [208] and [0488]; Figure 6). Further, Cheo et al teach the addition of regions that allow integration into eukaryotic chromosomes (e.g. transposable elements) (e.g. paragraph [0327]). Cheo et al teach a first target cassette comprising a polynucleotide to be substituted into the integration cassette flanked by two recombination sites (e.g. paragraphs [0045] and [0075]). Cheo et al do not teach a rec element encoding at least one recombinase activity that recognizes the recombinase recognition sites of the first integration cassette and second integration cassette.

Regarding claim 4, Cheo et al teach the use of the Flp recombinase protein to catalyze recombination between Frt sites (e.g. paragraphs [0047], [0048], [0055] and [0253]). Cheo et al do not teach a rec element encoding the Flp recombinase activity.

Regarding claim 5, Cheo et al teach the use of mammalian cells, yeast cells and bacterial cells (e.g. paragraph [0436]).

Regarding claim 6, Cheo et al teach the use of a first integration cassette comprising two, three, four etc. open reading frames that further comprise sequences that function as internal ribosome entry sites (IRES) (e.g. paragraph [0147]). The IRES allows the expression of two structural genes from a single transcript (i.e. bi-cistronic element) (e.g. paragraph [0544]).

Regarding claim 7, Cheo et al teach the use of a first integration cassette comprising a gene encoding a fusion protein comprising an N- or C-terminal tag such as an epitope tag or a six histidine tag (e.g. paragraph [0062]). Further, Cheo et al teach the use of recombination sites that comprise att sites, which comprise a TAG nucleic acid sequence (e.g. paragraph [0049]).

Regarding claim 8, Cheo et al teach a first target cassette comprising a first target gene and a first selectable marker gene that may be the same or different marker as compared to a selectable marker in the first integration cassette (e.g. paragraphs [0046] and [0148]).

Regarding claim 9, Cheo et al teach a first target cassette further comprising a plolycistronic element by including an IRES sequence to permit the bi-cistronic expression of two gene products from a single promoter (e.g. paragraphs [0143] and [0544]).

Regarding claim 10, Cheo et al teach the use of tagged proteins such as his tags (e.g. paragraph [0034]). Further, Cheo et al teach the use of recombination sites that comprise att sites, which comprise a TAG nucleic acid sequence (e.g. paragraph [0049]).

Regarding claim 11, Cheo et al teach the cellular expression system of claim 1 (discussed above) further comprising the following:

> In another specific aspect, the invention provides a method of cloning comprising providing at least a first nucleic acid molecule comprising at least a first and a second recombination site and at least a second nucleic acid molecule comprising at least a third and a fourth recombination site, wherein none of the first, second, third or fourth recombination sites is capable of recombining with any of the other sites, providing one or more vectors (e.g., two, three, four, five, seven, ten, twelve, etc.), comprising at least a fifth, sixth, seventh and eighth recombination site, wherein each of the fifth, sixth, seventh and eighth recombination sites are capable of recombining with one of the first, second, third or fourth recombination site, and conducting a recombination reaction such that at least said first and second molecules are recombined into said vectors. See paragraph [0154].

See also Figures 6 and 7 and paragraph [0075], for example. Further, Cheo et al teach a recombinase activity capable of recognizing the recombinase recognition sites of the second integration cassette and second target cassette (e.g. paragraphs [0055], [0196], [0253] and [0295]).

Regarding claim 12, Cheo et al teach the use of a second integration cassette comprising a gene encoding a fusion protein comprising an N- or C-terminal tag such as an epitope tag or a six histidine tag (e.g. paragraph [0062]). Further, Cheo et al teach the use of recombination sites that comprise att sites, which comprise a TAG nucleic acid sequence (e.g. paragraph [0049]).

Regarding claim 13, Cheo et al teach the use of a second integration cassette comprising two, three, four etc. open reading frames that further comprise sequences that function as internal ribosome entry sites (IRES) (e.g. paragraph [0147]). The IRES allows the expression of two structural genes from a single transcript (i.e. bi-cistronic element) (e.g. paragraph [0544]).

Regarding claim 14, Cheo et al teach a second target cassette comprising a first target gene and a first selectable marker gene that may be the same or different marker as compared to a selectable marker in the second integration cassette (e.g. paragraphs [0046] and [0148]).

Regarding claim 15, Cheo et al teach a second target cassette further comprising a plolycistronic element by including an IRES sequence to permit the bi-cistronic expression of two gene products from a single promoter (e.g. paragraphs [0143] and [0544]).

Regarding claim 16, Cheo et al teach the use of tagged proteins such as his tags (e.g. paragraph [0034]). Further, Cheo et al teach the use of recombination sites that comprise att sites, which comprise a TAG nucleic acid sequence (e.g. paragraph [0049]).

Regarding claim 17, Cheo et al teach the use of the system of claim 11 (described above) to construct nucleic acid molecules which encode more than one subunit of a multi-subunit complex such as an enzyme (e.g. paragraphs [0168] and [0354]).

Regarding claim 18, Cheo et al teach the use of the system of claim 11 (described above) to construct a multi-subunit complex that comprises an antibody molecule (e.g. paragraph [0168]).

Regarding claim 19, the recombination sites of the vectors function as "cloning sites" to clone recombinant molecules. Further, Cheo et al teach the inclusion of one or more restriction sites (e.g. multiple cloning sites) in the nucleic acid cassettes of the invention (e.g. paragraph [0140]).

Regarding claim 27, Cheo et al teach an integration cassette (e.g. starting molecule or Destination vector) comprising one or more (e.g. two) recombination sites, promoters, selectable markers, tags such histidine tags or green fluorescent protein, for example (e.g. paragraphs [0050], [0147], [0148], [208] and [0488]; Figure 6). Further, Cheo et al teach the addition of regions that allow integration into eukaryotic chromosomes (e.g. transposable elements) (e.g. paragraph [0327]).

Regarding claim 28, Cheo et al teach the use of tagged proteins such as his tags (e.g. paragraph [0050]). Further, Cheo et al teach the use of recombination sites that comprise att sites, which comprise a TAG nucleic acid sequence (e.g. paragraph [0049]).

Regarding claim 29, Cheo et al teach the use of internal ribosome entry sites (IRES) to make bi-cistronic expression elements where two structural genes are expressed from a single promoter (e.g. paragraphs [00147] and [0544]).

Cheo et al do not teach a rec element encoding at least one recombinase activity that recognizes the recombinase recognition sites of the first integration cassette and second integration cassette or a rec element encoding a flp recombinase activity.

Seibler et al teach a rec element, plasmid pOG44, encoding flp recombinase activity (e.g. page 1741, *(d) Recombination Prior to Integration*). Seibler et al teach that mammalian cells are capable of supporting recombinase mediated cassette exchange (RMCE) (as described above in the rejection under 35 U.S.C. § 102(b)), which will provide advantages including the ability to create reference integration sites characterized by their expression potential and long-term stability (e.g. page 1747, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cheo et al with regard to cellular expression system capable of performing site-specific recombinase mediated cassette exchange to include the rec element encoding flp recombinase taught by Seibler et al because Cheo et al teach it is within the ordinary skill in the art to perform recombination reactions *in vivo* in mammalian cells and Seibler et al teach the use of flp recombinase activity encoded by a plasmid to mediate site-specific recombination reactions *in vivo* in mammalian cells.

One would have been motivated to make such a modification in order to receive the expected benefit of identifying reference integration sites in the mammalian genome for reproducible levels of expression as taught by Seibler et al. Based upon the teachings of the

cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1, 4-19 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo et al Cheo et al (US Patent Application Publication No. 2002/0007051; see the entire reference) in view of Cox et al (US Patent No. 6,140,129; see the entire reference). This rejection has been included to address embodiments not covered by the combination of references set forth above.

The teachings of Cheo et al are described in the above rejection and are applied as before.

Cheo et al do not teach a rec element encoding at least one recombinase activity that recognizes the recombinase recognition sites of the first integration cassette and second integration cassette, or a rec element encoding a flp recombinase activity.

Cox et al teach a rec element encoding flp recombinase activity for expression in bacteria (e.g. column 6, lines 38-43). Further, the FLP system of Cox et al provides a method that can regulate recombination events and introduce FRT targets virtually anywhere in the chromosome (e.g. column 2, lines 6-14).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cheo et al with regard to cellular expression system capable of performing site-specific recombinase mediated cassette exchange to include the rec element encoding flp recombinase taught by Cox et al because Cheo et al teach it is within the ordinary skill in the art to perform recombination reactions *in vivo* in bacterial cells and Cox et al

teach the use of flp recombinase activity encoded by a plasmid to mediate site-specific recombination reactions *in vivo* in bacterial cells.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to regulate flp-mediated recombination events virtually anywhere in the bacterial chromosome as taught by Cox et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Citation of Relevant Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Schlake et al. Use of mutated FLP recognition target (FRT) sites for the exchange of expression cassettes at defined chromosomal loci. Biochemistry, Vol. 33, No. 43, pages 12746-12751, 1994.

Feng et al. Site-specific chromosomal integration in mammalian cells: Highly efficient CRE recombinase-mediated cassette exchange. J. Mol. Biol. Vol. 292, pages 779-785, 1999.

Storici et al. Molecular engineering with the FRT sequence of the yeast 2 μm plasmid: [*cir*°] segregant enrichment by counterselection for 2 μm site-specific recombination.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR, http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jennifer Dunston
Examiner
Art Unit 1636

jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER